UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,188	10/15/2001	Avi J. Ashkenazi	GNE.2630P1C8	5212

35489 7590 07/28/2005

HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,188	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-66 and 68-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-66 and 68-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 13, 2005 has been entered.

Claim Status

2. Claims 58-66 and 68-70 are pending in the instant application. Claims 58-62 have been amended as requested by Applicant in the Amendment filed April 8, 2005.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 58-62, 69 and 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claims 58-62, 69 and 70 are indefinite because claims they recite a "native sequence" polypeptide having at least 80%, 85%, 90%, 95% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 7. The specification teaches on pages 121-122 that:

"A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide specifically encompasses naturally-occurring or truncated or secreted forms of the specific PRO polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms and naturally-occurring allelic variants of the polypeptide."

However, it is not clear how one of ordinary skill in the art would be able to determine if a sequence is "a native sequence" or not by looking at it.

Maintained Rejections

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 58-66 and 68-70 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous office actions, mailed May 19, 2004, and February 8, 2005, and below.

Applicants' arguments (pages 6-27, Paper filed April 8, 2005) have been fully considered but are not deemed persuasive.

Applicants traverse the rejection and discuss the legal standard for utility on beginning on page 8, and starting on page 11 discuss the proper application of the legal standard. Applicants rely on the gene amplification data for patentable utility for the PRO274 protein, and explain the gene amplification assay of Example 114, in which PRO274 is amplified 2.0 fold to 3.053-fold

in three types of human primary lung tumors, which Applicants assert is significant and that the PRO274 gene has utility as a diagnostic of lung cancer.

Applicants submit the Declaration by Dr. Audrey Goddard, in which she states that a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer (page 11 of the response). The Goddard Declaration filed under 37 CFR 1.132, filed Oct. 4, 2004 is insufficient to overcome the rejection of claims 58-66 and 68-70 as set forth in the last Office action because: while the declaration and supporting references are convincing that the TaqMan realtime PCR method is very sensitive and can identify amplified genes, the claims are drawn to protein encoded by the PRO274 gene, and as discussed in the previous office action and below, it is not predictable that gene amplification results in increased mRNA expression, or that increased mRNA expression results in increased protein production.

Applicants at page 12 refers to the Gygi et al. and Pennica et al. references, and asserts that as a preliminary matter, it is not a legal requirement to establish a "necessary" correlation between an increase in copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is "imperative" to find evidence that protein levels can be accurately predicted, and the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Applicants submit that question is if it is more likely than not that a person of ordinary skill in the pertinent art would recognize a positive correlation between mRNA levels and protein levels. Applicants on page 12 submit that for the reasons previously set forth in the Applicants' response filed on November 8, 2004 that Pennica et al. does not show a lack of correlation

between gene (DNA) amplification and elevated mRNA levels. Applicants' arguments have been fully considered but are not deemed persuasive, for reasons of record in the office action mailed February 8, 2005.

On pages13-14, Applicant characterizes Gygi et al. as teaching that there is a general trend of increased protein levels from increased mRNA levels, and that at both low message levels and high message levels, the correlation coefficient was positive (10 copies/cell, 0.356 and abundant message, 0.94, respectively). Applicants also assert that Gygi et al. was studying steady-state yeast cells and not cancerous human cells, and that Gygi et al. admitted that "the present study has several potential sources of error related to the methods used to determine mRNA and protein expression levels." Applicants also point out that the authors admit that for the SAGE method, since more than 65% of the mRNA levels included in this study were calculated to 10 copies/cell or less, the error associated with these values may be quite large.

This has been fully considered but is not found to be persuasive. In the instant case, the specification provides data showing a very small increase in DNA copy number, approximately 2-3 fold, in a few tumor samples for PRO274. There is no evidence regarding whether or not the PRO274 mRNA or polypeptide levels are also increased in these tumor samples. Since the instant claims are directed to PRO274 polypeptide, it was important to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased in mRNA and polypeptide levels. Pennica et al. was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Gygi et al. was cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much

as 40-fold or even 50-fold were not uncommon. While Gygi et al. demonstrates that high levels of mRNA generally correlate with high levels of protein and that it appears that there is a general positive correlation between mRNA levels and protein levels, it has not been demonstrated that the PRO274 mRNA is over-expressed. Given the small magnitude by which the DNA copy number of PRO274 is increased, and the evidence provided by Gygi et al. and Pennica et al., it is clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with increased mRNA or polypeptide levels.

A more relevant reference, looking at transcript and encoded protein levels in human cancer cells, is Chen et al., Molecular and Cellular Proteomics, Vol. 1, pages 304-313, April 2002, who determined that in human carcinomas, for the majority of mRNAs and proteins, there is no correlation between transcript and protein levels. Chen et al. analyzed the abundance of 165 protein spots on two-dimensional gels corresponding to 98 individual genes in 76 lung adenocarcinomas and nine non-neoplastic lung tissues, and analyzed the abundance of the encoding mRNAs by microarrays. Among all 165 proteins the correlation coefficient values ranged from -.0467 to 0.442, and the mRNA/protein correlation coefficient also varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance (abstract). Although 21/98 genes showed a statistically significant correlation between mRNA and protein, the majority of the proteins did not correlate with mRNA levels (page 311, first column). The authors suggest that in the first group, expression is likely to be regulated at the transcriptional level, while in the second group, expression is regulated by other mechanisms. In addition to the analyses of the correlation of mRNA/protein within the same tumor samples, the authors also tested the global relationship

between mRNA and the corresponding protein abundance across all 165 protein spots using all 85 lung tissue samples, and observed a very wide range of normalized average protein and mRNA levels. The correlation coefficient generated was -0.025, and even for the 28 protein spots that showed a statistically significant correlation between individual mRNA and proteins, the correlation value was only –0.035 (see abstract and pages 311-312). The authors suggest that it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples, and teach that this conclusion is also supported by previous results from Anderson et al. (discussed below) and by Gygi et al. (discussed above), and in which both studies found a lack of correlation between mRNA and protein expression when average or overall levels were used.

Anderson et al., Electrophoresis, Vol. 18, pages 533-537, 1997, found that there was a poor correlation (0.48) between mRNA and protein levels in liver cells (abstract, page 535). They suggest that the two major phases of gene expression regulation (transcription through message degradation on the one hand, and translation through protein degradation on the other) are of approximately equal importance in determining the net output of proteins (page 536, left column). Anderson et al. also reanalyzed the set of data for plasma proteins secreted by the liver that was published by Kawamoto et al., (Gene, 1996, Vol. 16, pages 1977-1981), in which the mRNA-to-protein relationship for nine plasma proteins was 0.96. However, when albumin (which is well-separated from the cluster of the remaining eight and thus exercises a disproportionate influence on the correlation coefficient) was omitted from the calculation, the correlation coefficient is reduced to –0.19, which suggests a very poor correlation (page 536, right column).

Therefore, the art indicates that increased levels of transcript does not usually result in increased polypeptide levels.

On pages 15-17 of the response Applicant refers to three additional articles (Orntoft et al., Hyman et al. and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which are not likely to be in a chromosomal region which is highly amplified, given the low ΔCT values. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40), and though they found a correlation between increased protein levels and higher mRNA levels, only well resolved, abundant known proteins were analyzed (page 42). In the abstract it is stated:

"Because most proteins resolved by two-dimensional gels are unknown it was only possible to compare mRNA and protein alterations in relatively few cases of well focused abundant proteins."

Orntoft et al. also discuss the limitations of their methods at pages 44-45. Because Orntoft et al. only looked at a small sample of abundant proteins, it is not predictive that a small increase in transcript will result in increased protein abundance in general.

On page 16, Hyman et al. is discussed. Hyman et al. found that 44% of highly amplified genes showed mRNA over-expression (abstract). Polypeptide levels were not investigated, and

as discussed above, the art teaches that it is not predictive that an increase in mRNA will result in an increase in protein level. Therefore, Hyman et al. also do not support utility of the claimed polypeptides.

On pages 16-17 of the response, Applicant discusses Pollack et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. This has been fully considered but is not found to be persuasive. While showing on a gene by gene basis that in highly amplified DNA, it is likely that mRNA levels will be elevated. However, Pollack et al. did not investigate polypeptide levels, and as discussed above, the art teaches that it is not predictive that an increase in mRNA will result in an increase in protein level. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO274 proteins have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

On page 17, Applicants discuss the "substantial utility" standard, M.P.E.P. §2107.01, cites the following, "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of

ordinary skill in the art, do not impose a rejection based on lack of utility." Applicants' arguments have been fully considered but are not deemed persuasive. The M.P.E.P. §2107.01 recites: Deficiencies under the "useful invention" requirement of 35 U.S.C. 101 will arise in one of two forms. The first is where it is not apparent why the invention is "useful." This can occur when an applicant fails to identify any specific and substantial utility for the invention or fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966); In re Ziegler, 992 F.2d 1197, 26 USPQ2d 1600 (Fed. Cir. 1993). The second type of deficiency arises in the rare instance where an assertion of specific and substantial utility for the invention made by an applicant is not credible. While it is credible that the polypeptide could be used diagnostically, Applicants fail to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention, for the reasons discussed above.

On pages 18-19 of the response Applicants discuss the previously submitted declaration by Dr. Polakis. In the declaration, Dr. Polakis explains that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics, and that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Based on these experimental data and his vast scientific experience of more than, Dr. Polakis states that, for human genes, increased mRNA

levels typically correlate with an increase in abundance of the encoded protein, and he further confirms the "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

This has been fully considered but is not found to be persuasive. Only transcripts that are present in human tumor cells at *significantly* higher levels than in corresponding normal human cells were analyzed, which from the art would more likely result in increased protein abundance, as discussed above. It is important to note that the instant specification provides no information regarding increased mRNA levels of PRO274 in tumor samples relevant to normal samples. Only gene amplification data was presented. There is no information that the mRNA of PRO274 is significantly elevated in tumor cells.

On pages 19-20, Applicants assert that the case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew, and after evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument. Applicants also cite *In re* Alton, and discuss the Utility Examination Guidelines. Applicants assert that taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule, and that the teachings in the art and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels, and that the PRO274 polypeptides and antibodies have utility in the diagnosis of cancer. On pages 21-22, Applicants discuss the Hu et al. reference, and assert that Hu et al. only studies the

statistical analysis of micro-array data and not the gene amplification data, and their findings would not be directly applicable to the gene amplification data. Applicants also submit that the statistical analysis by Hu et al. is not a reliable standard because the authors manipulated various aspects of the input data, and the frequency of citation only reflects the current research interest of a molecule and but not the true biological function of the molecule. Applicants' arguments have been fully considered but are not deemed persuasive. The Journal of Proteome Research is a peer reviewed journal, and would not have been accepted for publication if the reviewers considered the methods and results suspect. Even though Hu et al. admits to some problems with the methodology, the Journal must have considered important enough to publish the article.

Applicants further submit that even assuming that Hu et al. provide evidence to support a true relationship, the conclusion in Hu et al. only applies to a specific type of breast tumor, and can not be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general. Applicants further assert that Hu et al. admits that it is likely that this threshold will change depending on the disease as well as the experiment, and the observed correlation was only found among ER-positive (breast) tumors and not ER-negative tumors, and that this may reflect a bias in the literature to study the more prevalent type of tumor in the population, and this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently.

Applicants' arguments have been fully considered but are not deemed persuasive. The Examiner agrees that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently; however, the totality of the art needs to be considered, and while some results indicate that gene amplification may result in increased

mRNA production, and that increased mRNA levels may result in higher protein levels, there is also data that indicate that such is not necessarily the case.

Applicants on page 12 assert that the PRO274 gene, similar to HER-2/neu gene disclosed in Hanna et al., is a tumor associated gene, and in the majority of amplified genes, the teachings of the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels, and therefore one of ordinary skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 polypeptide is concomitantly over-expressed. Applicants' arguments have been fully considered but are not deemed persuasive, for the reasons discussed above.

Applicants further assert that even if gene amplification does not result in over-expression of the protein, an analysis of the expression of the protein is useful in determining the course of treatment, as indicated by Dr. Ashkenazi in his Declaration. Applicants submit that simultaneously testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the protein is not over-expressed.

Applicants' arguments have been fully considered but are not deemed persuasive. It has not been demonstrated that the protein of the instant invention is differentially expressed in different tumors. If it was, the protein would have a specific and substantial utility for tumor classification, but the mere assertion that it may be differentially expressed does not provide a specific and substantial utility, and is an invitation to experiment.

One skilled in the art would do further research to determine whether or not the PRO274 polypeptide levels increased significantly in the tumor samples. The requirement for such further research requirements makes it clear that the asserted utility is not yet in currently

available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. For all of these reasons, the rejections are maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5.1 Claims 58-66 and 68-70 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

5.2 Claims 58-62 and 69-70 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention, for reasons of record in the office actions mailed May 19, 2004, and February 8, 2005, and below.

Applicants traverse the rejection on pages 24-27 and assert that as amended, the claims are drawn to native sequence polypeptides at least 80-99% identical to SEQ ID NO: 7. Applicants discuss the legal test for written description, and cites *Environmental Designs, Ltd. V. Union Oil Co.* Applicants assert that the polypeptide comprising the sequence set forth in SEQ ID NO: 7 meet the written description requirement of 35 U.S.C. 112, first paragraph, and thus the genus of native sequence polypeptides with at least 80% sequence identity to SEQ ID NO: 7, which possess the functional property of having a nucleic acid which is amplified in lung tumors would meet the requirement of 35 U.S.C. 112, first paragraph, as providing adequate written description. Applicants assert that the present application also describes methods for identifying genes which are amplified in lung cancer, and that by following the disclosure in the specification, one skilled in the art can easily test whether a gene encoding a native variant PRO274 protein is amplified in lung cancer; and also the specification further describes methods for the determination of percent identity between two amino acid sequences.

Applicants' arguments have been fully considered but are not deemed persuasive. In this case, the only factors present in the claim are functional, in that the protein of SEQ ID NO: 7 is encoded by a nucleic acid that is amplified in lung cancer. The specification discloses only a single sequence, SEQ ID NO: 7, that meets the limitations of the claims. It is clear that while there *could* be additional polypeptides that meet the limitations of the claims, that conception of such polypeptides has not occurred, and cannot occur until their actual isolation, as it is not predictable what additional mutations in SEQ ID NO: 7 would occur in nature and

further be amplified in lung cancer. As previously stated, one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQZII 1481 at 1483. In *Fiddes,* claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In this case, applicants have described a single sequence asserted to be associated with lung cancer, and propose to obtain coverage for all related sequences that have a similar association. There is no description of that class of compounds. This case is also analogous to that in *Amgen v. Chugai*, 18 USPQ 2d 1017 (1991), in which it was found that conception may not be achieved until reduction to practice in cases involving cloning genes. In this case, applicants have no conception of which of the thousands of possible polypeptides and nucleic acids that could encode the protein of SEQ ID NO: 7 would meet the limitation of being amplified in lung cancer.

Vas-cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. Chugai*

Pharmaceutical Co. L td., 18 USPQ2d 1016.

Therefore, polypeptides comprising the sequence set forth in SEQ ID NO: 7, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Rejections over Prior Art

Claim Rejections - 35 USC § 102 and § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6.1 Claims 58-66 and 68 remain rejected under 35 U.S.C. 102(b) as being anticipated by Ho et al., Science, Vol. 289, July 14, 2000, pages 265-270, for reasons of record in the previous Office Actions, mailed May 20, 2004, at page 11, mailed February 8, 2005 at page 14, and below.

6.2 Claims 69 and 70 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al., Science, Vol. 289, July 14, 2000, pages 265-270, in view of Hopp et al., U.S. Patent Number 5,011,912, for reasons of record in the previous Office Actions, mailed May 20, 2004, at pages 12-13, mailed February 8, 2005 at page 14, and below.

Applicants traverse the rejections and assert that the pending claims of the instant application are entitled to the effective filing date of February 11, 2000, since they rely on the gene amplification assay for patentable utility which was first disclosed in International Application NO. PCT/US00/03565, (discussed on pages 6-7 of the response), and therefore Ho

et al. is not prior art under 102(b) since its publication date is after the effective priority date of this application, and the instant claims are not obvious over Ho et al. in view of Hopp et al. Applicants' arguments have been fully considered but are not deemed persuasive, because the gene amplification assay fails to provide a patentable utility for the protein, for reasons discussed above, and the rejections are maintained.

It is believed that all pertinent arguments have been answered.

Conclusion

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (571) 272-0829.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

EILEEN B. O'HARA
PATENT EXAMINER